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Operation Everest II: comparison of four instruments for measuring blood O_2 saturation

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FORTE, VINCENT A., JR., MARK K. MALCONIAN, RICHARD L. BURSE, PAUL B. ROCK, PATRICIA M. YOUNG, LAURIE A. TRAD, BRUCE A. RUSCIO, JOHN R. SUTTON, CHARLES S. HOUSTON, AND ALLEN CYMERMAN. *Operation Everest II: comparison of four instruments for measuring blood O_2 saturation.* J. Appl. Physiol. 67(5): 2135–2140, 1989.—The bias and precision of four different methods for determining O_2 saturation (So_2) were evaluated during a study of hypobaric hypoxia conducted with seven male subjects exposed progressively over a 40-day period to simulated altitudes from sea level (760 Torr) to 8,840 m (240 Torr). So_2 of arterial and mixed venous blood samples were measured with the Instrumentation Laboratory 282 CO-oximeter (CO-OX), the Radiometer ABL-300 (ABL), and the Lex-O_2-Con-K (LEX). Noninvasive measurements of arterial So_2 were made with a Hewlett-Packard 47201A ear oximeter (EAR-OX). The CO-OX method was used as a secondary standard for comparison with the other methods because it has been validated against the classical Van Slyke method over a wide physiological range (Maas et al., *Clin. Chim. Acta* 29: 303–309, 1970). The LEX results most closely approximated but consistently underestimated those of the CO-OX: LEX = 0.93 CO-OX −0.86, standard error of the estimate (SEE) = 5.17, r = 0.98, n = 670. The ABL method appeared to combine two linear trends: for So_2 >75%, ABL = 0.84 CO-OX +14.4, SEE = 1.77, r = 0.97, n = 369; <75%, ABL = 0.98 CO-OX +5.9, SEE = 4.44, r = 0.97, n = 486. The EAR-OX results were found to approximate those of the CO-OX at So_2 values only >65%: EAR-OX = 1.07 CO-OX −6.12, SEE = 7.71, r = 0.98, n = 326. In a separate experiment, the CO-OX, LEX, and ABL methods were used to determine the So_2 of human blood previously tonometered with eight gases of known O_2 concentrations to produce saturations from 13.3 to 99.7%. This test confirmed the CO-OX as being the most accurate and precise of the three methods. Of the other two, the ABL was the most precise. The LEX although of lesser precision had the better accuracy, approximating that of the CO-OX.

altitude; hypobaric hypoxia; mixed venous saturation; tonometry

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MEASUREMENT of the degree of O_2 saturation (So_2) of oxyhemoglobin is essential in clinical medicine and research for monitoring of oxygenation by the cardiorespiratory system. Arterial O_2 saturation (Sa_{O_2}) is used to assess the efficiency of the respiratory system in the uptake of alveolar O_2, whereas mixed venous saturation ($S\bar{v}_{O_2}$) reflects the results of O_2 delivery and metabolic usage at the tissue level. Because diseases of the pulmonary and cardiovascular systems can interfere with O_2 uptake and delivery, knowledge of both arterial and mixed venous saturation is required to monitor the progression of those diseases. Saturations as low as 60% in arterial blood and 20% in mixed venous blood have been reported in patients with chronic lung disease or congenital heart disease, even at normal atmospheric pressures. Clinical and research monitoring instruments must therefore have bias and precision known over a wide range of saturation and, if measuring saturation directly, be of known accuracy.

Sa_{O_2} can be monitored by either invasive or noninvasive techniques. Invasive methods require the removal of a blood sample from the body under anaerobic conditions, followed by measurement of O_2 saturation by either direct or indirect methodologies. The newer invasive methods have a number of advantages over the classical direct Van Slyke method (7), which is the primary standard: less blood for a single determination, shorter analysis time, and easier operation. Saturation can be determined directly from blood either gasometrically (2, 11, 15), spectrophotometrically (4, 6, 12, 14), or galvanically (16, 18). Indirect determinations require measurement of whole blood Po_2, Pco_2, and pH followed by estimation of So_2 from an algorithm (17). This method depends on how closely each subject's O_2-hemoglobin equilibrium curve matches the standard normal curve (5) and therefore exhibits some degree of intersubject variability.

Determinations of arterial So_2 (but not venous) can be made noninvasively by measuring the transdermal absorption of light by hemoglobin in the blood flowing through the superficial vasculature of the ear or the finger. One such type of instrument is an optoelectronic device that computes Sa_{O_2} by analyzing the absorption characteristics of eight wavelengths of light as it passes through the pinna of the ear to identify different ratios of oxyhemoglobin to deoxyhemoglobin.

Comparison of newer direct spectrophotometric or galvanic methods against the classical gasometric Van Slyke method has shown a high degree of agreement in the range of saturations from 50 to 100% in nonsmokers (11, 18), but comparisons for lower saturation levels have not been reported. Reasonably close agreement between arterial saturation values determined by noninvasive and invasive methods have been obtained when Sa_{O_2} exceeds

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70% but not below ~70% saturation (12–14).

Recently a hypobaric chamber study entitled "Operation Everest II" (8) provided a unique opportunity to determine both arterial and venous saturation values in humans, both at rest and during exercise, at a number of simulated altitudes ranging from sea level [inspired partial pressure of O_2 (P_{IO_2}) = 159 Torr] up to 8,840 m (P_{IO_2} = 43 Torr). The opportunity was available at each altitude to compare one noninvasive and three invasive methods over a wide physiological range of S_{O_2}.

MATERIALS AND METHODS

Operation Everest II (OEII) was a study of acclimatization to hypoxia conducted with seven physically fit males (21–31 yr) who were gradually decompressed over a 40-day period from sea level to a final P_{IO_2} of 43 Torr (8). The study took place in the hypobaric chamber at the US Army Research Institute of Environmental Medicine in Natick, MA (elevation 50 m). All subjects were nonsmokers, had no cardiopulmonary abnormalities, and were medically screened before providing informed consent at the start of the study. More specific study details are available elsewhere (8).

Initial base-line measurements of Sa_{O_2} and $S\bar{v}_{O_2}$ were made at rest and during cycle ergometer exercise for all subjects. Blood samples taken from subjects at rest and during exercise were then obtained at barometric pressures of 483 Torr (3,660 m), 429 Torr (4,572 m), 347 Torr (6,100 m), and 282 Torr (7,620 m) for all subjects, 258 Torr (8,235 m) for four subjects, and, finally, at 240 Torr (8,840 m) for three subjects. True mixed venous blood was obtained from a prepositioned Swan-Ganz catheter in the pulmonary artery, and arterial blood was obtained from an 18-gauge catheter in either the radial or brachial artery. Samples were drawn into sterile airtight 5-ml glass syringes (matched sets) containing 0.2 ml beef lung heparin (1,000 IU/ml, Upjohn, Kalamazoo, MI) to prevent clotting. The samples were drawn anaerobically after a volume of blood was discarded to eliminate any contamination from dead-space fluids and were immediately placed on ice. All analyses were completed within 30 min. Just before each determination, each sample was mixed well and divided anaerobically for analyses in triplicate by each instrumental method.

Sa_{O_2} determinations were made with three instruments: *1*) Lex-O_2-Con-K (LEX, Lexington Instruments, Lexington, MA); *2*) CO-oximeter (CO-OX, IL-282, Instrumentation Laboratory, Lexington, MA), and *3*) ABL-300 Blood Gas System (ABL, Radiometer, Copenhagen, Denmark). Saturation was measured directly with the CO-OX and ABL, whereas O_2 content was determined with the LEX and then S_{O_2} was calculated using the modified Siggard-Anderson equation (17): S_{O_2} = (O_2 content)/(1.37 × hemoglobin concentration) × 100%. The hemoglobin concentration was measured by a hemoglobinometer (Coulter Electronics, Hialeah, FL), which was selected because it was not influenced by choice of anticoagulant. All blood samples were performed in triplicate. Noninvasive determinations of arterial saturation were also made with an eight-wavelength ear oximeter (EAR-OX, Hewlett-Packard, Lexington, MA) at the same time as blood samples were obtained.

All instrumentation was calibrated, operated, and maintained in accordance with the procedures specified in the operator's manual furnished by the manufacturer. For the ABL, an O_2-scavenging sodium dithionite solution was used during calibration to obtain 0% S_{O_2}. Accuracy and linearity of the ABL were further maintained by using Radiometer Qualicheck solutions to confirm the calibration of all electrodes throughout normal, acidemic, and alkalotic ranges before each series of blood gas measurements. In the CO-OX, particular care was taken to ensure that no traces of blood were retained in the analysis chamber; periodic checks of its internal hemoglobin measurement performance were made with a synthetic hemoglobin standard (15 g/ml) for comparison with the Coulter results. The EAR-OX was standardized by a set of internal electrical references (equivalent to 20, 80, and 100% S_{O_2}), which were verified before each exercise test.

The results obtained from the ABL, LEX, and EAR-OX methods were compared with those from the CO-OX, because the CO-OX has been widely used as a secondary standard for measurement of Sa_{O_2} and has been previously validated against the Van Slyke method (2, 11, 16, 18). In each comparison to the CO-OX, the best-fit line was determined from all paired data and then tested for nonlinearity. BMDP software packages on a Vax 11/780 computer (Digital Equipment, Maynard, MA) were used to calculate means, slopes, *y*-intercepts, and correlation coefficients and to perform analyses of variance. For each comparison, the entire range of saturation data was divided into groups of 10% saturation (decades). The midpoints of each decade were then used for determination of bias and precision. Bias was determined by the offset of the LEX, ABL, and EAR-OX results from those of the CO-OX. To give a reliable estimate of precision of the tested method, the standard deviation of the least squares regression line was determined at the midpoint of each decade.

Subsequent to the OEII study, a separate experiment was conducted to determine the accuracy of the CO-OX, ABL, and LEX in analyzing blood drawn from a nonsmoker, which had been equilibrated in a large bubble tonometer (Dynex-3M, Analytical Products, Belmont, CA) for 45–60 min with eight separate gas mixtures of known O_2 concentration. All gas mixtures used in tonometry were assayed by the Scholander microtechnique (15) and were selected to produce the entire range of saturations (13.3–99.7%), calculated by the Siggard-Anderson equation. Each tonometered sample was analyzed in triplicate (one small sample in duplicate) by all three direct methods to determine each method's response without any complicating physiological changes in pH, P_{CO_2}, and hemoconcentration induced by the combination of altitude exposure and physical exercise.

RESULTS

The results from the LEX, ABL, and EAR-OX are plotted against those for CO-OX in Figs. 1–3, respectively. The relationship between the ABL and the CO-OX results (Fig. 1), after correction for carboxyhemoglobin (HbCO) and methemoglobin (MetHb), was linear (ABL = 0.91 CO-OX + 8.88, r = 0.99). Two of the

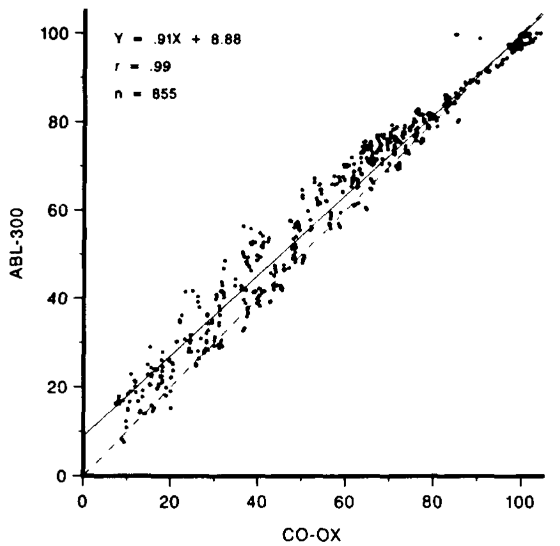

FIG. 1. Comparisons of arterial and venous O_2 saturations obtained simultaneously with ABL-300 (*ordinate*) and CO-oximeter (*abscissa*) in 7 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise. Solid line, line of regression; dashed line, line of identity.

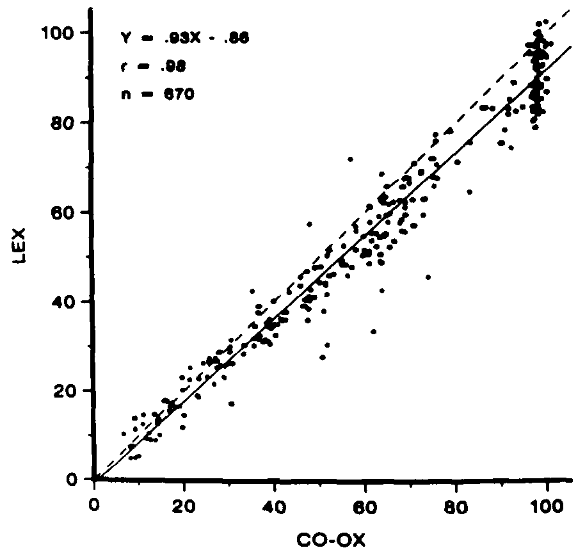

FIG. 2. Comparisons of arterial and venous O_2 saturations obtained simultaneously with Lex-O_2-Con (*ordinate*) and CO-oximeter (*abscissa*) in 7 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise. Solid line, line of regression; dashed line, line of identity.

original 857 paired values were removed for excessive scatter (any value ≥6 standard deviations from the mean of its neighbors in the range of ±5% saturation). The obvious second-order component was tested and found to be nonsignificant ($0.20 < P < 0.50$), but the variability was found to be much less above 75% saturation. As a result, separate linear trends were calculated for paired values above and below 75% saturation. Above 75%, ABL = 0.84 CO-OX + 14.4, r = 0.97, standard error of the estimate (SEE) = ±1.77, n = 369. Below 75%, ABL = 0.98 CO-OX + 5.9, r = 0.97, SEE = ±4.44, n = 486.

The LEX results (Fig. 2) were found to be linearly related to, but to underestimate, the CO-OX results throughout the entire range of saturation values (LEX = 0.93 CO-OX − 0.86, r = 0.98). Of the original 673 paired values, 3 were removed for excessive scatter. The SEE was ±5.17, indicating a moderate degree of variability.

The relationships between the EAR-OX and the CO-OX values were plotted for saturations ≥45% (Fig. 3). The overall regression was EAR-OX = 1.11 CO-OX − 10.2, SEE = ±5.00, r = 0.97, n = 420. The variability was markedly greater <65%, so the regression was recalculated for points above 65% (EAR-OX = 1.07 CO-OX − 6.12, SEE = ±7.71, r = 0.98, n = 326). No values were removed for excessive scatter.

Estimates of both the bias (offset) from the CO-OX results and precision (variability about the offset) of the ABL, LEX, and EAR-OX were made at the midpoint of each "decade" of CO-OX saturation (10.5–20.4%, 20.5–30.4%, . . . , 90.5–100%), except in the first decade (from 0 to 10.4%) where there were too few measurements. The entire range of saturation from 10 to 100% was included for the LEX and ABL, but only the decades from 60 to 100% were included for the EAR-OX. Bias within each decade was estimated by calculating the difference between the independent variable (LEX, ABL, or EAR-OX) from its paired CO-OX value and then determining the mean of these differences within each decade and plotting it at the decade midpoint. The standard deviation about each mean difference was used as an estimate of the precision, although the variance or the average deviation about the mean also could have been used. The resultant plots are shown in Fig. 4, *A–C* for the ABL, LEX, and EAR-OX, respectively.

As seen in Fig. 4*A*, the ABL method consistently overestimated the CO-OX results, except in the highest decade. The ABL method had the least bias and the greatest precision at the high end of the saturation range. *Decades 2–7* showed bias ranging from +3.9 to +6.2%, whereas *decades 8* and *9* were +2.1 and +1.5% (much less than their next lower neighbors), while the highest decade was −1% (Table 1). There was no trend in the precision with increasing saturation in *decades 2–9*: precision varied from ±2.4 to ±5.9%; the 10th decade, how-

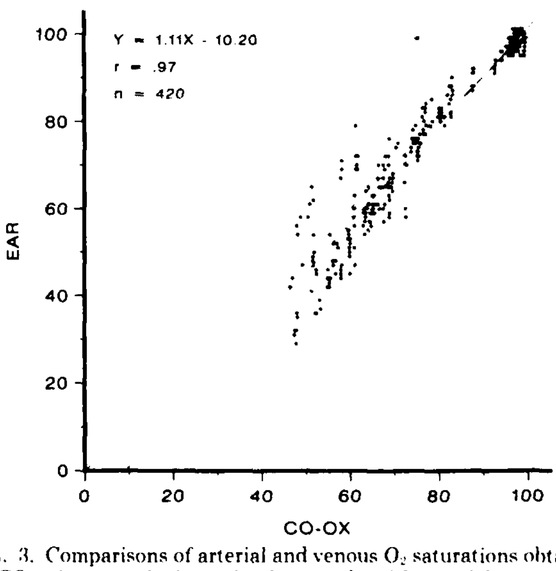

FIG. 3. Comparisons of arterial and venous O_2 saturations obtained from CO-oximeter (*abscissa*) simultaneously with arterial saturations with ear oximeter (*ordinate*) in 7 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise.

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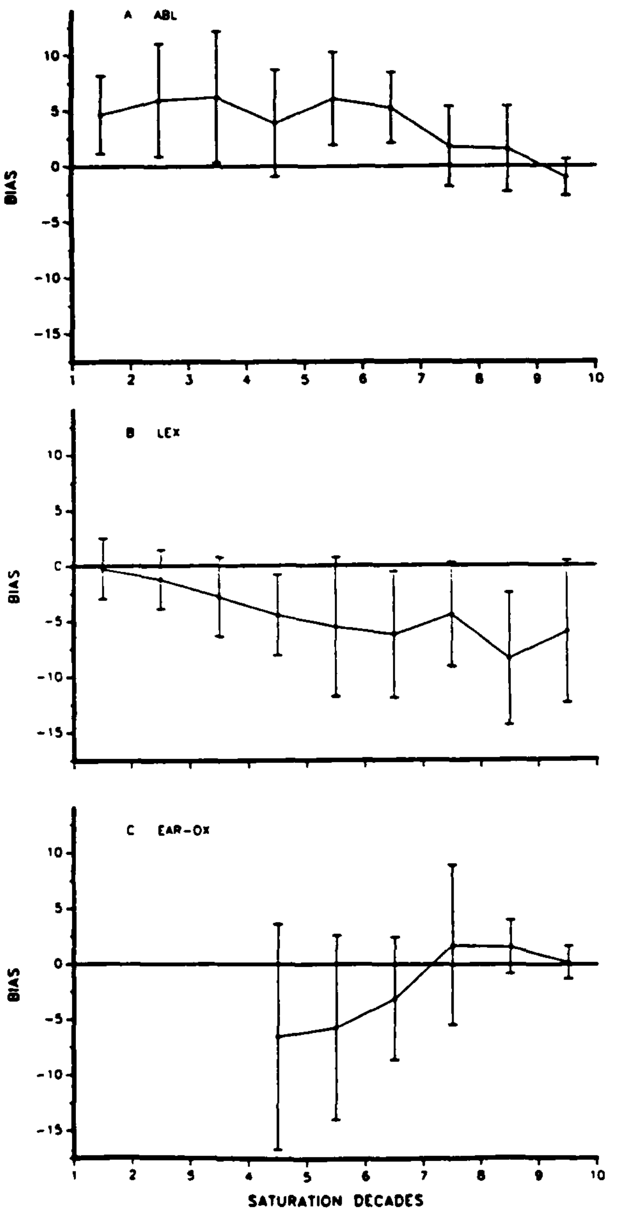

FIG. 4. Data from Radiometer ABL-300 (ABL, *A*), Lex-O_2-Con-K (LEX, *B*), and ear oximeter (EAR-OX, *C*) showing bias (offset) and precision (standard deviation) at midpoint of each decade of O_2 saturation.

ever, was ±1%, less than one-half of the next lower value.

The LEX consistently underestimated the CO-OX throughout the entire range of saturations and markedly more so as saturation increased (Fig. 4*B*). The least bias and best precision for the LEX method was in the lower four of the plotted decades. From the second to the seventh decade the negative bias became increasingly more pronounced, from nearly 0 to 6%; above the 8th decade the bias varied, in the range of −4.5 to −8.4% (Table 1). The precision also decreased as saturation increased: *decades 2–5* ranged from ±2.7 to 3.6%, whereas *decades 6–10* were even worse, ranging from ±4.7 to 6.4%.

Although the EAR-OX method has been recommended for determining arterial saturations from 70–100% (7), the bias and precision were plotted from the 5th through the 10th decades to visualize any trends outside the

TABLE 1. *Comparison of bias and precision of test instruments used to measure O_2 saturation at various simulated high altitudes*

Saturation (decade)	Mean Deviation (bias)	Std Deviation (precision)	Sample Size	Significance
		ABL vs. CO-OX		
2	4.66	3.51	57	<0.01
3	5.95	5.08	53	<0.01
4	6.21	5.89	78	<0.01
5	3.86	4.80	66	<0.01
6	6.07	4.18	60	<0.01
7	5.25	3.18	128	<0.01
8	2.08	2.37	89	<0.01
9	1.54	3.86	52	<0.01
10	−0.96	1.02	255	<0.01
		LEX vs. CO-OX		
2	−0.26	2.73	55	NS
3	−1.23	2.67	43	<0.05
4	−2.81	3.57	71	<0.01
5	−4.48	3.63	49	<0.01
6	−5.54	6.27	60	<0.01
7	−6.25	5.68	113	<0.01
8	−4.45	4.69	42	<0.01
9	−8.44	5.95	13	<0.01
10	−6.01	6.41	207	<0.01
		EAR-OX vs. CO-OX		
5	−6.53	10.14	12	<0.05
6	−5.70	8.30	44	<0.01
7	−3.11	5.53	80	<0.01
8	1.70	7.17	46	<0.01
9	1.59	2.41	30	<0.01
10	0.18	1.47	208	NS

ABL, Radiometer ABL-300; CO-OX, CO-oximeter; LEX, Lex-O_2-Con-K; EAR-OX, ear oximeter. Decades are divided into 10% intervals for all comparisons over the entire saturation range (10–100%), *decade 2* = 10.5–20.4%, *decade 3* = 20.5–30.4%, . . . *decade 10* = 90.5–100%. Significance is the probability that mean deviation equals zero.

recommended range (Fig. 4*C*). The EAR-OX was found to overestimate the CO-OX results in *decades 8–10* but only by 0.2–1.7% (Table 1) and to progressively underestimate them as saturation decreased. EAR-OX precision was best in *decades 9* and *10* (±2.4 and 1.5%, respectively), intermediate in *decades 7* and *8* (±5.5 and 7.2%, respectively), and poorest in *decades 5* and *6* (±8.3 and 10.1%, respectively). Interestingly, although the bias in the eighth decade was similar to that of the ninth, the precision was much worse, despite that decade's having a greater sample size.

Figure 5 shows the results of the second experiment in which the three direct methods (ABL, LEX, and CO-OX) determined SO_2 in blood samples that had been carefully tonometered against eight gases of known O_2 composition. These gases yielded calculated saturations (17) from 13.3 to 99.7%. The ABL method (Fig. 5*A*) overestimated the actual saturations from 0.8 to 5.0%, except at 99% saturation. The precision (standard deviations) generally ranged from ±0.8 to 0.3%, except at the two lowest saturations, where they were ±0.08 to 1.0%. The LEX method (Fig. 5*B*) underestimated the actual saturations throughout the range, from −0.7 to −7.6%, with precision varying from ±0.2 to 5.2%. Figure 5*C* shows the CO-OX method to slightly underestimate actual saturations from −0.8 to −2.3% in the middle ranges,

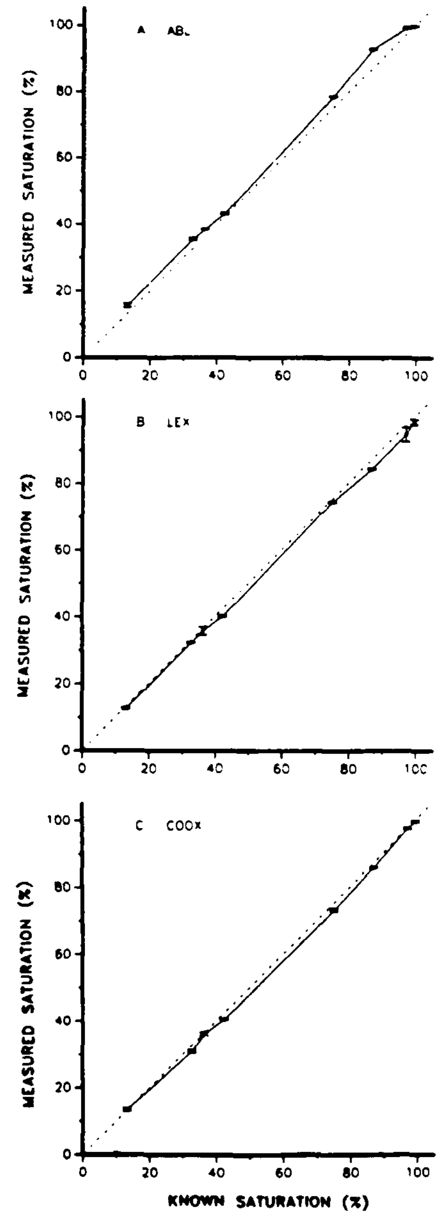

FIG. 5. Measurements of arterial O_2 saturation with ABL (*A*), LEX (*B*), and CO-OX (*C*) with human blood, which was tonometered with gases of known O_2 concentration: 1.06, 2.52, 4.40, 4.72, 10.04, 15.96, 19.56, and 20.96% (13.3–97.8% saturation). Bars, ±SE of replicates. See legend of Fig. 4 for definition of abbreviations.

where the So_2 curve changes the most rapidly, but to be indistinguishable from them at the upper and lower ends. The precision of the CO-OX method ranged from ±0.2 to 0.8%.

DISCUSSION

There was wide disparity in the amount of time required to perform So_2 analyses using the three different methods. In the same period of time, 890 samples were analyzed by the ABL method, 857 by the CO-OX method, but only 670 by the LEX method, which therefore became the limiting factor in the paired comparisons. The CO-OX method was selected as the "independent" variable against which the other techniques were measured because of prior validations against the Van Slyke blood gas analysis method (4, 11). The LEX method was found to be linearly related to the CO-OX method throughout the entire range of saturations but to consistently underpredict the CO-OX results. Plotting of the negative bias and its associated variability showed the underprediction to progressively increase as saturation increased and the greatest variability (standard deviations between ±4.7 and 6.4%) to occur at the upper end of the saturation range, from 50 to 100%. Below 50% saturation, bias decreased toward 0 as saturation declined while the precision was markedly better, ranging from 2.8 to 3.6% saturation. Thus the LEX results very nearly matched those of the CO-OX at low saturations, an impression that was reinforced by the results of the separate tonometry experiment.

The ABL results were neither as consistent nor as readily interpreted as the LEX results. Although the nonlinear component of the ABL vs. CO-OX relationship was found to be nonsignificant, there appeared to be two separate linear components. The first component, >75% saturation, had a slope of <1, which crossed the line of identity at 88% and had a very small scatter (standard deviation ~±1% in the 10th decade). The second component comprised the results <90%. It was essentially parallel to the line of identity but had the greatest degree of bias (7%) of any method and the poorest precision overall (standard deviations from ±2.4 to 5.9%).

Prior comparison with the Van Slyke method suggested that the EAR-OX method be used only for arterial saturations of >70% (7). In the current study, only the results of >80% saturation were found to be linearly related to those of the CO-OX method; measurements of <80% tailed off rapidly (Fig. 4), showing bias downward from +2 at 75% saturation to −6 at 45%. Furthermore, the precision was poor at all points downward from 75%, from 5 to 10% (SD). The standard deviations were <3% for >80% saturation, quite similar to those of the ABL method and much better than those of the LEX method at the same saturation.

The identical EAR-OX method was used by West et al. (19) to measure Sa_{O_2} during the 1982 American Medical Research Expedition to Mt. Everest (AMREE, 19).

TABLE 2. *Comparison of Sa_{O_2} from two studies with an ear oximeter*

Altitude, m	PI_{O_2}, Torr	*n*	Sa_{O_2}, at Rest	Sa_{O_2} in Exercise, %	
				60 W	90–120 W
Operation Everest II					
6,100	63	7	75±1	64±2	57±2
7,620	49	5	68±2	57±2	53±2
8,840	43*	5	51±2	44±1	38±1
American research expedition to Everest					
6,300 m Air	63	6	73†	70	65
6,300 m 16% O_2	49	6	66†	57	54
6,300 m 14% O_2	43	2	64†	54	51

Sa_{O_2}, arterial O_2 saturation; PI_{O_2}, inspired partial pressure of O_2; AMREE, American Medical Research Expedition to Everest. A Hewlett-Packard ear oximeter was used. * Atmospheric O_2 elevated >40.5 Torr, equivalent altitude of 8,050 m. † Extrapolated from West et al. (19), using Siggard-Anderson equation to calculate Sa_{O_2} from Po_2 of AMREE at 6,300 m with 16% O_2 (8,050 m) and with 14% O_2 (8,840 m). Equivalent to Po_2 measured in OEII at 7,620 and 8,840 m, respectively.

In that study, measurements were made while subjects breathed air and gas mixtures of 14 and 16% at 6,300 m, which produced altitude equivalents of 6,300, 8,050, and 8,840 m, respectively. Our results agree with those of the AMREE, both at rest and during exercise at 60 W during air and 16% O_2 breathing at 6,300 m (Table 2) but are of markedly lower saturation than those at the same PI_{O_2} (43 Torr) when the AMREE subjects breathed 14% O_2. The metabolic rates at rest and during 60-W exercise should have been very similar, if not identical, in both groups. The reasons for the saturation difference at 43 Torr are not clear, but they are not likely to be related to Sa_{O_2} measurement differences, given the close similarity in results in subjects breathing air and 16% O_2. The lower saturation observed in OEII subjects, at PI_{O_2} = 43 Torr, implies much greater extraction at the tissue level or lesser oxygenation in the lung. One obvious difference is that the OEII subjects were progressively acclimatized down to the inspired PI_{O_2} of 43 Torr, whereas the AMREE subjects were acutely exposed to the hypoxic gas mixture at 43 Torr and may have hyperventilated more. Another difference is that the OEII subjects were not exposed to the same overall physical, climatic, and situational stress as the group on the Mt. Everest and may have undergone a less intensive overall acclimatization.

The tonometered blood experiment confirmed the supposition that the CO-OX method could be used as a "secondary standard" to which the other methods could be compared. It was the most accurate of the three invasive methods, slightly underestimating only the middle ranges of saturation and then by only <2%. Throughout the entire range of saturations it was the most precise. The LEX method appeared to be nearly as accurate as the CO-OX method, underestimating the known saturations in the mid- and upper ranges by <2%, but the precision of the LEX method was clearly poorest of the three throughout the entire saturation range. The ABL method appeared to be similar in precision to the CO-OX but overestimated the tonometered saturations throughout the entire range. This was the worst accuracy of the three methods, up to 3% error at >70% saturation. Because the LEX method is much slower than the other two, requiring almost twice as long per sample, the CO-OX method appears to be best suited when a large number of samples must be analyzed and a high degree of both accuracy and precision are required.

This paper is one of a series entitled "Operation Everest II."

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